

JUL 11 2007

Patent

Attorney Docket No. 1034284-000003**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of)	MAIL STOP AF
Ignacio Blanco Blanco)	Group Art Unit: 1652
Application No.: 10/549,759)	Examiner: ROSANNE KOSSON
Filed: September 19, 2005)	Confirmation No.: 6945
For: USE OF ALPHA-1 ANTITRYPSIN)	
FOR THE PREPARATION OF)	
MEDICAMENTS FOR THE)	
TREATMENT OF FIBROMYALGIA)	

DECLARATION OF IGNACIO BLANCO BLANCO UNDER § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ignacio Blanco Blanco, hereby declare as follows:

1. I am a citizen of Spain, and reside at Oviedo, Spain.
2. My education and professional history are outlined in my attached curriculum vitae (Attachment A).
3. I am the sole inventor in the referenced application, and submit this Declaration in support thereof.
4. Attached hereto are print-outs dated March 22, 2007 from the Alpha One International Registry (AIR) (see Attachment B). (The attached print-outs are from the Spanish AATD Registry, which is a corresponding national registry of the AIR. The AIR International Registry is not accessible as doctor users have access only to their corresponding national registry.)
5. The printed information discloses the information in the Registry relating to the two patients referred to in the cited Blanco reference (two sisters, designated here as patients 205 and 206). The Registry information relating to those

Buchanan Ingersoll & Rooney PC
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two patients is confidential information that is not publicly available, even to those with general access to the Registry. Rather, it is accessible only by the registering doctor. Specifically, the information is available only to the doctor who has registered the particular patients, and the Registry requires that the doctor provide a confidential user name and access code (or key code). The confidential listings are available only to the accessing doctor, and only when such confidential and personal information has been entered.

6. As can be seen in attachment C, the Registry information made available to Dr. Blanco, even after entering his confidential user name and key code, includes only that corresponding to his nine patients. The information pertaining to those patients includes the following: registry number, release date, patient initials, date of birth, sex, pulmonary function (F_{ev1} Post (Basal)), FVC Post Basal, substitutive treatment (yes or no), and whether monitoring is performed.

7. The accessing doctor may consult the data of his/her patients by clicking the Registry number and accessing a new page containing demographic and clinical data. See Attachments D & E (files with the data of the two sister patients with alpha-1 antitrypsin deficiency, patient numbers 205 and 206, in Spanish with translations attached).

8. The Registries record only the data appearing in the presented database fields. Thus, in Dr. Blanco's patients, the only data having been reported are those shown in the database. Any additional information, e.g., that regarding the effect of substitutive treatment for AAT Deficiency or use of AAT for other conditions such as fibromyalgia, has never been reported and thus is not accessible from the Registry. The information presented within the Registry relates only to the treatment

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of congenital AAT deficiency. There is no field for the entry of information relating to other maladies such as fibromyalgia, and no such information has been introduced. Accordingly, there is nothing within the Registry - whether public or private - that relates to the incidence or possible treatment of fibromyalgia in those patients.


9. Although it has been stated that the patients have received substitutive treatment, the nature of that treatment and its results were never entered into the Registry, nor was that information publicly available.

10. Also attached hereto is a publication entitled "Ongoing Research in Europe: Alpha One International Registry (AIR) Objectives and Development", *Eur Respir J* (2007) 29:582-586 (Attachment F). This reference discusses generally the development and objectives of the Alpha One International Registry in response to the recommendation of the World Health Organization. The reference describes the protocol of handling of information, emphasizes confidentiality of that information and patient characteristics, and focuses primarily on the geographic distribution of the various forms of Alpha One Trypsin Deficiency. As stated in the reference, the information provided is carefully controlled. Additionally, there is no mention of the disclosure of substitutive treatment, nor is there any suggestion that the use of substitutive treatment for other, unrelated conditions, is even entered into the system or publicly accessible. This confirms that information such as is relied upon in the referenced application was not included in the AIR registry, and was not publicly available.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

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statements and the like so made are punishable by fine or imprisonment, or both,
under Section 1001 of Title 18 of the United States Code and that such willful false
statements may jeopardize the validity of the application or any patent issued
thereon.

Date: 29/06/2007 By: 
Ignacio Blanco Blanco

ATTACHMENT A

- CURRICULUM VITAE -

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**Name:** Ignacio BLANCO BLANCO**Citizenship:** Spanish**Date of birth:** 05/23/1944**Identity No:** 11 338 723-E**Address:** C/ Comandante Caballero 10, 1º A, 33005
Oviedo, Asturias, Spain**Phone No:** +34 985 252481**E-mail:** Ignacio.blanco@sespa.princast.es**PRESENT POSITION (from 12/31/1977)**

Head of the Section of Respiratory Diseases, Department of Internal Medicine, Hospital Valle del Nalón (Polígono de Riaño s/n, 33920, Langreo, Asturias, Spain, Tel.: +34 985 652000, Fax: +34 985 652006)

PREVIOUS POSITIONS:

Institution	Date	Position held
Departament of Internal Medicine, Hospital Virgen de la Arrixaca, Murcia, Spain	06/04/1976- 12/30/1977	Head of the Section of Respiratory Diseases, Department of Internal Medicine
Department of Respiratory Diseases, National Institute of Silicosis, Oviedo, Spain	1976	Head of the Section of Respiratory Diseases
Department of Respiratory Diseases, National Institute of Silicosis, Oviedo, Spain	1971-1975	Associate MD
Department of Internal Medicine, Hospital General de Asturias, Oviedo, Spain	1967-1971	Trainee, MD
Medical School, University of Valladolid, Spain	1961-1967	MD

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DISTINCTIONS:

- 05/24/2007** Member of the *Programa de Intensificación de la Actividad Investigadora de Facultativos de Atención Especializada* (i.e. intensive research programme for medical specialists), Health Institute Carlos III, Spanish Ministry of Health and Consumption
- 2001-present** Treasurer and Member of the Permanent Board of the Official Medical Association of Asturias, Spain
- 1996-present** Founding Member of ASTURPAR (i.e. Society of Respiratory Diseases in Asturias, Spain)
- 1995-present** Member of the European Respiratory Society (ERS)
- 1993-present** Advisor for the Expert Committee of the Spanish Registry of Alpha-1 Antitrypsin Deficiency (AATD) patients
- 1973-present** Full Member of SEPAR (i.e. Spanish Society of Respiratory Diseases)
- 2002-2004** Member of the Expert Committee of the International Consortium (Spain-USA-South America) for the research on Alpha-1 Antitrypsin Deficiency (AATD)
- 1982-1988** Assistant Professor for practical training, Medical School, University of Oviedo, Asturias
- 1978-1982** Member of the Spanish Evaluation Technical Commission for Coal
- 1976-1978** Associate Professor of Medical Pathology, Medical School, University of Murcia
- 1976-1978** Full Member of the International Union Against Tuberculosis (IUT)

SCIENTIFIC AWARDS:

- 2007** ASTURPAR Award on Scientific Research, Best publication on Alpha-1 Antitrypsin Deficiency (AATD)
- 2005** ASTURPAR Award on Scientific Research, Best presentation on COPD
- 2004** ASTURPAR Award on Scientific Research, Best publication on Alpha-1 Antitrypsin Deficiency (AATD)
- V Award on Scientific Research of the Hospital Valle del Nalón, Asturias, Spain, Best publication on Alpha-1 Antitrypsin Deficiency (AATD)
- 2003** IV Award on Scientific Research of the Hospital Valle del Nalón, Asturias, Spain, Best poster on Alpha-1 Antitrypsin Deficiency (AATD)
- 2002** ASTURPAR Award on Scientific Research, Best publication Alpha-1 Antitrypsin Deficiency (AATD)

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| 2001 | Award on Scientific Research of the Hospital Valle del Nalón, Asturias, Spain, Alpha-1 Antitrypsin Deficiency (AATD) |
| 1993 | V <i>García Cosío</i> Award on Scientific Research of the National Institute of Silicosis, Oviedo, Spain, Best research on Alpha-1 Antitrypsin Deficiency (AATD) in Asturias |
| 1985 | I Award in Scientific Research of the Hospital Cabueñes, Gijón, Asturias, Best bronchial asthma publication together with Mario Argüelles Toraño, MD |

PUBLICATIONS (1970-2007):

1. Janciauskiene S, Stevens T, **Blanco I**. New insights into the biology of α 1-antitrypsin and its role in chronic obstructive lung diseases. *Current Respiratory Medicine Reviews* 2007; 3(2): 147-158
2. **Blanco I**, FJ de Serres, S Janciauskiene, D. Arbesú, EF. Bustillo, V. Cárcaba, I Nita, A Astudillo. Estimates of the prevalence and number of fibromyalgia syndrome patients and their Alpha-1-antitrypsin phenotypic distribution in ten countries. *Journal of Musculoskeletal Pain* 2007; Volume 15, 000-000 (at press)
3. **Blanco I**, Arbesú D., Al Kassam D; de Serres F; Fernández-Bustillo E, Rodríguez Menéndez C. Alpha1-antitrypsin polymorphism in fibromyalgia patients from the Asturias Province in Northern Spain: A significantly higher prevalence of the PI*Z deficiency allele in patients than in the general population. *Journal of Musculoskeletal Pain* 2006 14 (3);5-12
4. de Serres, **Blanco I**, Bustillo EF. Estimating the risk for alpha-1 antitrypsin deficiency among COPD patients: evidency supporting targeted screening. *COPD: International Journal of COOPD*, 2006.;3(3):133-9
5. **Blanco I**, Janciauskiene S, Astudillo A, Domínguez F, Bustillo EF, Nita I. Chapter 1 (pag: 1-37): Fibromyalgia and alpha-1 antritrypsin. *New research in Fibromyalgia*. Nova Science Publisher, INC.,New York. 2006
6. *Normativa SEPAR N. 43*: Normativa sobre el diagnóstico y tratamiento del deficit de alfa-1-antitripsina. [Article in Spanish] Vidal R, **Blanco I**, Casas F, Jordi R, Miravittles M. Ediciones Doyma, Barcelona, 2006
7. Vidal R, **Blanco I**, Casas F, Jordi R, Miravittles M; Committee on the National Registry of Individuals with Alpha-1 Antitrypsin Deficiency. [Guidelines for the diagnosis and management of alpha-1 antitrypsin deficiency][Article in Spanish] *Arch Bronconeumol*. 2006;42(12):645-659
8. I **Blanco**, de Serres F, Fernandez-Bustillo E, Lara B, Miravittles M. Estimated numbers and prevalence of PI*S and PI*Z alleles of α 1-antitrypsin deficiency in European countries. *European Respiratory Journal* 2006; 27 (1): 77-84

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9. de Serres J, Luisetti M, Ferrarotti I, **Blanco I**, Fernández-Bustillo E. Implications of regional differences in the distribution of the PIS and PIZ deficiency alleles on diagnosis and management of alpha-1 antitrypsin deficiency in Italy. *Monaldi Archives of Chest Diseases* 2005; 63 (3): 133-141
10. de Serres, F.J., **I. Blanco**, E.F. Bustillo. Health implications of alpha-1-antitrypsin deficiency in Sub-Sahara African countries and their emigrants in Europe and the New World. *Genetics in Medicine*. 2005 ;7(3):175-84
11. Gavahami S, Hashemi M, Shahriari HA, Bajestani SN, de Serres F, Moghaddam EM, Kamezi M, Alavian SM, Taheri M, **Blanco I**, Fernández-Bustillo E. Alpha-1-antitrypsin phenotypes and HLA-B27 typing in uveitis patients in southeast Iran. *Clin Biochem*. 2005;38(5):425-32
12. **Blanco I**, FJ de Serres, E F-Bustillo, D Al Kassam, D Arbesú, C Rodríguez, J.C. Torre. Alpha 1-Antitrypsin and fibromyalgia: new data in favour of the inflammatory hypothesis of fibromyalgia. *Medical Hypotheses (Oxford)* 2005; 64: 759-769
13. **I. Blanco**, E F-Bustillo, F.J. de Serres; D. Alkassam; C. Rodríguez. Déficit de alfa-1 antitripsina en España (variantes deficientes PI*S y PI*Z): prevalencia estimada y número de sujetos deficientes calculados para cada fenotipo. [Article in Spanish] *Medicina Clínica (Barc)* 2004;123(20):761-765
14. **I. Blanco**, H. Canto, F.J. de Serres, E-F Bustillo, MC Rodríguez. Alpha-1 Antitrypsin replacement therapy controls fibromyalgia symptoms in 2 patients with PI ZZ Alpha-1 Antitrypsin deficiency. *The Journal of Rheumatology* 2004; 31 (10): 2082-2085
15. de Serres, F.J., **I. Blanco**, E.F. Bustillo (2003) Genetic Epidemiology of Alpha-1 Antitrypsin Deficiency in Australia, Canada, New Zealand, and the United States of America. *Clinical Genetics* 2003; 64: 1-16
16. de Serres, F.J., **I. Blanco**, E.F. Bustillo (2003) Genetic Epidemiology of Alpha-1 Antitrypsin Deficiency in Southern Europe: France, Italy, Portugal, and Spain. *Clinical Genetics* 2003; 63: 1818-1829
17. **Blanco I**, EF Bustillo, MC Rodríguez. Distribution of a1-antitrypsin PI S and PI Z frequencies in countries outside Europe: a meta-analysis. *Clinical Genetics* 2001; 60: 431-44
18. **Blanco I**, E Fernández, EF Bustillo. Alpha-1-antitrypsin PI phenotypes S and Z in Europe: an analysis of the published surveys. *Clinical Genetics* 2001; 60: 31-41
19. **Blanco I**, E Fernández. a1-antitrypsin Pi phenotypes S and Z in Spain: an analysis of the published surveys. *Respiratory Medicine* 2001; 95: 109-114

- CURRICULUM VITAE -

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20. **Blanco I**, E Fernández, MC Rodríguez, A Fernández.. Frecuencias alélicas del gen de la alfa-1 antitripsina en la población general de una comarca de Asturias. [Article in Spanish] *Med Clin (Barc)* 1999; 133: 366-370
 21. **Blanco I**, H Canto, F Carro. Normativa SEPAR de EPOC: propuesta de cambio de la clasificación. [Article in Spanish] *Arch Bronconeumol* 1998; 34: 409-410
 22. **Blanco I**, Sala Blanco J, Canto Argiz H, Carro del Camino F. Gorostidi Pérez J. Pleurodesis con sangre autóloga: resultados en una serie de 17 casos con más de un año de seguimiento. [Article in Spanish] *Rev Clin Esp* 1997; 197: 406-410
 23. **Blanco I**, Canto H., Carro F., Fuentes J., Sala J. Pleurodesis con sangre del propio paciente: resultados iniciales en 14 casos. [Article in Spanish] *Arch Bronconeumol* 1996; 32: 230-236
 24. Antuña AS, Marrón MG, Garcia JM, Martinez MA, Sánchez A, **Blanco I**. Amiloidosis traqueobronquial localizada. Utilidad de la tomografía computarizada. [Article in Spanish] *Arch. Bronconeumol* 1995; 31:540-542
 25. **Blanco I**, H Canto, F Carro. Bronquiectasias en pacientes con déficit severo de alfa-1 antitripsina: ¿una asociación frecuente?. [Article in Spanish] *Arch Bronconeumol* 1994; 29: 473
 26. Carro F, **Blanco I**. Granulomatosis pulmonar por talco y celulosa en un paciente VIH-positivo, con hemoptisis e infiltrado pulmonar unilateral, adicto a fármacos orales por vía endovenosa. [Article in Spanish] *Arch Bronconeumol* 1993; 29:297-299
 27. **Blanco I**, Miranda J, Motto A., Bustillo EF et al. Contribución de la tomografía axial computerizada al estudio la pneumoconiosis de los mineros del carbón en estadios precoces. [Article in Spanish] *Arch Bronconeumol* 1993; 29: 274-280
 28. **Blanco I**, ML Menéndez, F Carro. Bronquiectasias extensas como manifestación única de déficit de alfa-1 antitripsina. [Article in Spanish] *Arch Bronconeumol* 1992; 28: 253
 29. **Blanco I**, F Carro, H Canto. Carcinoma bronquial y renal simultáneos. [Article in Spanish] *Arch Bronconeumol* 1991;27: 386
 30. Argüelles M, **I Blanco** . Inflammatory bronchial polyps associated with asthma. *Arch Intern Medicine* 1983; 143:570-571
 31. **Blanco I**, L. Palenciano. Influencia de la broncofibroscopia en los gases en sangre arterial. [Article in Spanish] *Arch Bronconeumol* 1976; 12: 76-78
 32. Arroyo F, Marin R, **Blanco I**, Fernández J. Melanoma maligno de coroides, ginecomastia y nódulo mamario metastásico. [Article in Spanish] *Rev Clin Esp* 1970; 119:153-156

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JOURNAL REFEREE:

- *Stroke*
- *Clinical Genetics*
- *Collegium Antropolologicum*
- *European Respiratory Journal*
- *Journal of Pharmaceutical and Biomedical Analysis*
- *Archivum Immunologiae et Therapiae Experimentalis*
- *Iranian Journal of Biotechnology*
- *The Journal of Musculoskeletal Pain*
- *Respiratory Medicine*

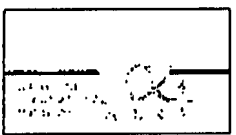
GRANTS AND RESEARCH PROJECTS:

10/17/2006. Grant, Programa de Promoción de la Investigación Biomédica y en Ciencias de la Salud (i.e State programme for the promotion of biomedical and health scientific research), **Health Institute Carlos III**, Spanish Ministry of Health and Consumption, main researcher in the project **PI061798: Estudio de las isoformas de la alfa-1-antitripsina, citocinas proinflamatorias, metaloproteasas y marcadores de estrés oxidativo en el músculo de pacientes con fibromialgia** (Study of Alpha-1 Antitrypsin isoforms, proinflammatory cytokines, metalloproteases and oxidative stress biomarkers in the muscle of Fibromyalgia patients)

2004-present: Collaborator in the development of the *Proyecto IDDEA* for the identification and diagnosis of Alpha-1 Antitrypsin Deficiency (AATD). National Screening Programme for Alpha-1 Antitrypsin Deficiency in COPD patients, based on the determination of the Alpha-1 Antitrypsin (AAT) genotype in the Central Laboratory of the Spanish AAT Registry (Hospital Vall d'Hebron, Barcelona).

2001-2007. Epidemiological study carried out together with Frederick DE SERRES, PhD (National Institute of Environmental Health Sciences, Research Triangle Park, Chapel Hill, North Carolina, USA). Frequency, prevalence and number estimation of Alpha-1 Antitrypsin Deficiency subjects (S and Z alleles) worldwide. Results, published in aforementioned publications (21.-25.), have been obtained for Europe, Northern America, Australia and New Zealand, Sub-Saharan Africa and Asia.

ATTACHMENT B

	REGISTRO ESPAÑOL DE PACIENTES CON DÉFICIT DE ALPA-1 ANTITRIPSINA	<div style="border: 1px solid black; padding: 5px;"> ACCESO AL REGISTRO Usuario: Clave: <input type="button" value="Solicitar claves"/> <input type="button" value="Entrar ->"/> </div>				
El desarrollo de esta aplicación ha sido posible gracias a la colaboración de Q.F BAYER, una beca del área de IRTS de la SEPAR y una beca (FIS:02/10003) del Fondo de Investigaciones Sanitarias (FISS).						
PRESENTACIÓN	PUBLICACIONES	ENLACES DE INTERÉS	INFORMACIÓN PARA PACIENTES	PROYECTO IDDEA	BOLETINES REDAAT	CONTACTAR
<p>FUNDACIÓN DEL REGISTRO ESPAÑOL DEL DAAT</p> <p>Debido a la escasa prevalencia del DAAT, surgió la necesidad de acumular información derivada del estudio de grupos de pacientes con esta enfermedad. El Registro Español de pacientes con DAAT se fundó el 13.04.1993, pero debido al pequeño número de pacientes que se esperaba reclutar, no nació con el objetivo de ser una alternativa a los ensayos clínicos para conocer la eficacia del tratamiento, sino que el propósito inicial del Registro fue:</p> <p>OBJETIVOS DEL REGISTRO</p> <ol style="list-style-type: none"> 1. Conocer las características y la frecuencia del DAAT en España. 2. Establecer normativas adaptadas a nuestro país sobre el tratamiento y seguimiento de pacientes con el déficit. 3. Ofrecer información a los médicos que tratan a estos pacientes en toda España. 4. Incrementar el conocimiento y el interés por esta "no tan rara" enfermedad e intentar disminuir el infradiagnóstico o el retraso en el conocimiento del DAAT. 5. Recoger información acerca de la evolución funcional, la frecuencia del tratamiento sustitutivo y la posible aparición de efectos adversos con este tratamiento. 6. Ofrecer soporte técnico para la determinación del fenotipo PI y si es necesario del genotipo en aquellos individuos con sospecha de DAAT. 						
<p>ORGANIZACIÓN DEL REGISTRO</p> <p>Desde su origen, el Registro es un grupo de trabajo del Área IRTS (Insuficiencia Respiratoria y Trastornos de Sueño) de la SEPAR (Sociedad Española de Neumología y Cirugía Torácica). Lo componen dos coordinadores, un Comité Asesor y 64 centros participantes distribuidos por toda España y Andorra.</p> <p>La base de datos se encuentra en el centro coordinador, en el que también existe el laboratorio central que ofrece la posibilidad de determinar el fenotipo PI y en casos especiales el genotipo mediante secuenciación del DNA.</p> <p>El Comité Asesor se reúne periódicamente para evaluar y analizar la evolución de la base de datos del Registro y actualizar las normativas referentes al tratamiento sustitutivo con AAT y el seguimiento de los pacientes.</p> <p>Coordinadores:</p> <p>Marc Miravittles . Servicio de Neumología, Hospital Clínic i Provincial de Barcelona.</p> <p>Rafael Vidal. Servicio de Neumología, Hospital General Vall d'Hebron. Barcelona</p> <p>Comité asesor:</p> <p>Juan Carlos Barros-Tizón. Vigo</p> <p>Ignacio Blanco. Langreo</p> <p>Ana Bustamante. Torrelavega</p> <p>Francisco Casas. Granada</p> <p>Carlos Escudero. Oviedo</p> <p>Pedro P. España. Galdakao</p> <p>Malte Martínez. Madrid</p> <p>Gestión del registro español</p> <p>Beatriz Lara. Barcelona</p>						

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Laboratorio central del registro

Rosendo Jardí y Francisco Rodríguez-Frías. Servicio de Bioquímica, Hospital General Vall d'Hebron.

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**SPANISH REGISTRY OF PATIENTS
WITH ALFA-1 ANTITRYPSIN DEFICIENCY**

REGISTRY ACCESS	
User Key	
Asking for key	Log in

FOUNDING OF THE SPANISH REGISTRY OF AATD

Owing to the scarce prevalence of AATD, the necessity arose to accumulate information derived from studying groups of patients with this condition. The Spanish Registry of patients with AATD was founded on 13.04.1993, however, owing to the small number of patients that were to be recruited, it was not set up with the objective of being an alternative to clinical trials in order to discover the effectiveness of the treatment. Instead, the initial aim of the Registry was:

OBJECTIVES OF THE REGISTRY

1. To discover the characteristics and frequency of AATD in Spain.
2. To establish rules adapted to our country on the treatment and follow-up of patients with this deficit.
3. To offer information to doctors who treat these patients in Spain.
4. To widen the knowledge and interest in this condition (which is not so rare) and try to reduce the infradiagnosis of or delays in recognising AATD.
5. To collect information on the functional evolution, the frequency of alternative treatments or the possible appearance of side affects with this treatment.
6. To offer technical support for determining the Pi phenotype and if necessary the genotype of those individuals suspected of having AATD.

ORGANISATION OF THE REGISTRY

From the outset, the Registry is a working group in the IRTS (Insufficient Respiratory and Sleep Disorder) Area of SEPAR (Spanish Society of Pneumology and Thoracic Surgery). It comprises of two coordinators, an Advisory Committee and 64 participating centres distributed through Spain and Andorra.

The database can be found in the coordinating centre, where the central laboratory is also located, which offers the possibility of determining the Pi phenotype and, in special cases, the genotype by means of DNA sequencing.

The Advisory Committee meets regularly in order to evaluate and analyse the evolution of the Registry's database and update the rules in reference to alternative treatment with AAT and patient follow-up.

Coordinators:

Advisory Committee:

Management of the Spanish registry:

Registry's Central Laboratory:

ATTACHMENT C

REGISTRO ESPAÑOL DE PACIENTES CON DEFICIT DE ALFA-1 ANTITRIPSINA																																																																																																																								
<div> <input type="checkbox"/> REGISTRO DE PACIENTES <div> <input type="checkbox"/> Registrar nuevo paciente <input type="checkbox"/> Listado de pacientes </div> </div> <div> <input type="checkbox"/> Situación actual del Registro <input type="checkbox"/> Estudios en fase de realización o desarrollo <input type="checkbox"/> Publicaciones <input type="checkbox"/> Preguntas abiertas <input type="checkbox"/> Proteólisis <input type="checkbox"/> Trypsina <input type="checkbox"/> Envíos de muestra </div> <div> <input type="checkbox"/> SALIR DEL REGISTRO >> </div>																																																																																																																								
<p>pendientes: Faltan datos de seguimiento semestral. Por favor, cumplimente los datos del formulario de seguimiento del paciente.</p> <table border="1"> <thead> <tr> <th>Nº registro</th> <th>Fecha alta</th> <th>Iniciales</th> <th>Nacimiento</th> <th>Sexo</th> <th>Fav1 Post (Basal)</th> <th>FVC Post (Basal)</th> <th>Tratamiento sustitutivo</th> <th>Perdido</th> <th>Exitus</th> <th>Seguimientos</th> </tr> </thead> <tbody> <tr> <td>205</td> <td>04/02/2002</td> <td>EAF</td> <td>12/06/1951</td> <td>Mujer</td> <td>2,00</td> <td>2,36</td> <td>Si</td> <td></td> <td></td> <td>Pendiente</td> </tr> <tr> <td>206</td> <td>04/02/2002</td> <td>RAF</td> <td>12/04/1947</td> <td>Mujer</td> <td>1,40</td> <td>2,30</td> <td>Si</td> <td></td> <td></td> <td>Pendiente</td> </tr> <tr> <td>207</td> <td>04/02/2002</td> <td>CFG</td> <td>14/06/1935</td> <td>Mujer</td> <td>1,80</td> <td>2,20</td> <td></td> <td></td> <td></td> <td>Pendiente</td> </tr> <tr> <td>215</td> <td>05/02/2002</td> <td>AAG</td> <td>01/01/1941</td> <td>Hombre</td> <td>2,60</td> <td>4,10</td> <td></td> <td></td> <td></td> <td>Pendiente</td> </tr> <tr> <td>216</td> <td>05/02/2002</td> <td>HPG</td> <td>24/08/1940</td> <td>Mujer</td> <td>2,40</td> <td>2,80</td> <td></td> <td></td> <td>Si</td> <td>Pendiente</td> </tr> <tr> <td>217</td> <td>05/02/2002</td> <td>JCGC</td> <td>22/12/1940</td> <td>Hombre</td> <td>0,80</td> <td>2,30</td> <td>Si</td> <td></td> <td></td> <td>Pendiente</td> </tr> <tr> <td>218</td> <td>05/02/2002</td> <td>EFF</td> <td>24/07/1928</td> <td>Mujer</td> <td>1,60</td> <td>2,50</td> <td></td> <td></td> <td>Si</td> <td></td> </tr> <tr> <td>219</td> <td>05/02/2002</td> <td>MPVT</td> <td>15/05/1954</td> <td>Hombre</td> <td>1,50</td> <td>2,30</td> <td>Si</td> <td></td> <td>Si</td> <td></td> </tr> <tr> <td>221</td> <td>13/04/2004</td> <td>MAMD</td> <td>24/03/1962</td> <td>Hombre</td> <td>1,35</td> <td>2,40</td> <td></td> <td></td> <td></td> <td>Pendiente</td> </tr> </tbody> </table>											Nº registro	Fecha alta	Iniciales	Nacimiento	Sexo	Fav1 Post (Basal)	FVC Post (Basal)	Tratamiento sustitutivo	Perdido	Exitus	Seguimientos	205	04/02/2002	EAF	12/06/1951	Mujer	2,00	2,36	Si			Pendiente	206	04/02/2002	RAF	12/04/1947	Mujer	1,40	2,30	Si			Pendiente	207	04/02/2002	CFG	14/06/1935	Mujer	1,80	2,20				Pendiente	215	05/02/2002	AAG	01/01/1941	Hombre	2,60	4,10				Pendiente	216	05/02/2002	HPG	24/08/1940	Mujer	2,40	2,80			Si	Pendiente	217	05/02/2002	JCGC	22/12/1940	Hombre	0,80	2,30	Si			Pendiente	218	05/02/2002	EFF	24/07/1928	Mujer	1,60	2,50			Si		219	05/02/2002	MPVT	15/05/1954	Hombre	1,50	2,30	Si		Si		221	13/04/2004	MAMD	24/03/1962	Hombre	1,35	2,40				Pendiente
Nº registro	Fecha alta	Iniciales	Nacimiento	Sexo	Fav1 Post (Basal)	FVC Post (Basal)	Tratamiento sustitutivo	Perdido	Exitus	Seguimientos																																																																																																														
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SPANISH REGISTRY OF PATIENTS
WITH ALFA-1 ANTITRYPSIN DEFICIENCY

Registration No.	Release date	Initials	Date of birth	Sex	Fevl Post (Basal)	FVC Post (Basal)	Alternative treatment	Lost	Exitus	Follow-up
205										
206										
207										

ATTACHMENT D

REGISTRO ESPAÑOL DE PACIENTES CON DEFICIT DE ALFA-1 ANTITRIPSINA	
<input checked="" type="checkbox"/> REGISTRO DE PACIENTES <input type="checkbox"/> Registrar nuevo paciente <input type="checkbox"/> Listado de pacientes <input type="checkbox"/> Situación actual del Registro <input type="checkbox"/> Estudios en fase de realización o desarrollo <input type="checkbox"/> Publicaciones <input type="checkbox"/> Preguntas abiertas <input type="checkbox"/> Prolastina <input type="checkbox"/> Trypsone <input type="checkbox"/> Envíos de muestra <input type="checkbox"/> SALIR DEL REGISTRO >>>	<div>MODIFICAR DATOS DE PACIENTE</div> <div>Ver seguimientos + Nuevo seguimiento +</div> <p>Por favor, siga las siguientes reglas para la introducción de datos:</p> <p>Utilice el signo PUNTO para indicar decimales: (Ej.: 34.203)</p> <p>Indique las fechas siempre con el formato dd/mm/aaaa: (Ej: 23/02/2001)</p> <p>PACIENTE Nº: 205 INICIALES PACIENTE: EAF</p> <p>Código de país: E Fecha de inclusión: 04/02/2002</p> <p>DEMOGRAFÍA Fecha de nacimiento: 12/06/1951 dd/mm/aaaa Sexo: Female Altura: 148 Unidades de altura: Cm Peso (kg): 58 kilos</p> <p>TABAQUISMO Fumó alguna vez? No Edad de inicio: años Dejó de fumar? Edad en que dejó de fumar: años Consumo medio de cigarrillos diarios: Consumo medio de cigarros diarios: Pipe - g/semana:</p> <p>MOTIVO DE LA DETERMINACIÓN DE AAT Motivo para determinación de AAT: Family screening Fenotipo: Z Otro fenotipo deficiente: Fecha del diagnóstico del déficit AAT: 15/01/1994 dd/mm/aaaa</p> <p>HISTORIA CLÍNICA Enfermedad pulmonar: Yes Bronquitis crónica: No Enfisema: Yes Asma: Yes Bronquiectasias: Yes Otra enfermedad pulmonar? No Especificar: Edad al inicio de los síntomas respiratorios: 40 Años: Meses: Síntoma principal: Dyspnoea on exertion</p>

OTROS DIAGNÓSTICOS No

Diagnóstico 1: fibromialgia reumática

ICD código diagnóstico 1: Ver Tabla de códigos

ICD versión:

Diagnóstico 2:

ICD código diagnóstico 2: Ver Tabla de códigos

ICD versión:

Diagnóstico 3:

ICD código diagnóstico 3: Ver Tabla de códigos

ICD versión:

Trasplante de pulmón: Fecha del trasplante de pulmón: dd/mm/aaaa

Reducción de volumen pulmonar: Fecha de reducción de volumen pulmonar: dd/mm/aaaa

Trasplante de hígado: Fecha del trasplante de hígado: dd/mm/aaaa

Ha sufrido neumonías?

En caso afirmativo, ¿Cuántas veces?:

Número desconocido

DATOS TC

TC del tórax: No Fecha del TC de tórax: 12/05/1994 dd/mm/aaaa

TRATAMIENTO ACTUAL

Medicación para la enfermedad pulmonar: Yes Oxigenoterapia domiciliar: No

TRATAMIENTO SUSTITUTIVO

Alguna vez ha recibido tratamiento sustitutivo? Yes Fecha de inicio: 10/07/1995 dd/mm/aaaa

Dejó el tratamiento? No Fecha de interrupción: dd/mm/aaaa

FUNCIONALISMO PULMONAR

Fecha de las primeras pruebas disponibles: 10/07/1994 dd/mm/aaaa

FEV1 pre-broncodilatador (L): 2 litros FEV1 post-broncodilatador (L): 2 litros

FVC pre-broncodilatador (L): 2,36 litros FVC post-broncodilatador (L): 2,36 litros

VC lenta pre-broncodilatador (L): 2,37 litros VC lenta post-broncodilatador (L): 2,37 litros

Fecha de las pruebas más recientes: 10/12/2001 dd/mm/aaaa

FEV1 pre-broncodilatador (L): 1,9 litros FEV1 post-broncodilatador: 1,9 litros

FVC pre-broncodilatador (L): 2 litros FVC post-broncodilatador: 2 litros

VC lenta pre-broncodilatador (L): 2 litros VC lenta post-broncodilatador: 2 litros

KCO (%): %

ENZIMAS HEPÁTICAS

Enzimas hepáticas: Yes

Fecha de determinación: 06/06/1999 dd/mm/aaaa

ALAT/SGOT Elevada: No
 ASAT/SGPT Elevada: No
 GGT Elevada: No
 FA Elevada: No

DATOS CUESTIONARIO ST GEORGE

Puntuación total
 SGRQ:

HISTORIA LABORAL

Trabaja actualmente: No

SI NO,
 especifique el motivo: Other

Muestra de plasma? Yes

Muestra de sangre total? Yes

FECHA FINAL

Fecha de fallecimiento: dd/mm/aaaa

Causa de muerte:

Otra causa, especificar:

Se realizó autopsia:

Modificar Paciente

Cancelar

Patient N°: 205

PATIENT'S INITIALS: EAF

Country code: E

Inclusion date: 04/02/2002

DEMOGRAPHICS

Date of birth:

12/06/1951 dd/mm/yyyy

Sex:

Female

Height

148

Height units

Cm

Weight (kg):

58

kilos

SMOKING HABITS

Have you ever smoked? No

Age started:

years old

Have you given up smoking?

Age stopped:

years old

Average daily consumption of cigarettes:

Average daily consumption of cigars:

Pipe - g/week:

REASON FOR DETERMINING AAT

Reason for determining AAT

Family screening

Phenotype:

Z

Other deficient phenotype:

Date of diagnosis of AAT deficit:

15/01/1994

dd/mm/yyyy

CLINICAL HISTORY

Lung disease

Yes

Chronic bronchitis

No

Emphysema

Yes

Asthma

Yes

Bronchiectasis

Yes

Other lung disease

No

Specify

Age respiratory symptoms started

Years old

40

Months

Principal symptom

Dyspnoea on exertion

Other diagnosis	No		
Diagnosis 1: rheumatic fibromyalgia			
ICD code			
Diagnosis 1	See Code Table	ICD version	
Diagnosis 2			
ICD Code			
Diagnosis 2	See Code Table	ICD version	
Diagnosis 3			
ICD Code			
Diagnosis 3	See Code Table	ICD version	
Lung transplant		Date of lung transplant:	dd/mm/yyyy
Reduction in lung volume		Date of reduction of lung volume:	dd/mm/yyyy
Liver transplant:		Date of liver transplant:	dd/mm/yyyy
Have you suffered from pneumonia?			
If so, how many times?		Unknown number	
TC data			
Thorax TC:	No	Date of Thorax TC:	12/05/1994 dd/mm/yyyy
CURRENT TREATMENT			
Medication for lung disease	Yes	Home oxygen therapy:	No
ALTERNATIVE TREATMENT			
Have you received an alternative treatment	Yes	Start date:	10/07/1995 dd/mm/yyyy

Did you stop treatment?	No	Interruption date	dd/mm/yyyy
-------------------------	----	-------------------	------------

PULMONARY FUNCTIONING

Date of first tests available	10/07/1994	dd/mm/yyyy	
FEV1 pre-bronchodilator 2 (L):	litres	FEV1 post-bronchodilator (L)	2 litres
FVC pre-bronchodilator 2.36 (L):	litres	FVC post-bronchodilator (L)	2.36 litres
Slow VC pre-bronchodilator 2.37 (L):	litres	Slow VC post-bronchodilator (L)	2.37 litres
Date of most recent tests	10/12/2001	dd/mm/yyyy	
FEV1 pre-bronchodilator 1.9 (L):	litres	FEV1 post-bronchodilator (L)	1.9 litres
FVC pre-bronchodilator 2 (L):	litres	FVC post-bronchodilator (L)	2 litres
Slow VC pre-bronchodilator 2 (L):	litres	Slow VC post-bronchodilator (L)	2 litres
KCO (%):	%		

HEPATIC ENZYMES

Hepatic enzymes: Yes

Date of determination: 06/06/1999
dd/mm/yyyy

High
ALAT/SGOT No

High
ASAT/SGPT No

High GGT No

High FA No

ST GEORGE QUESTIONNAIRE DATA

Total score
SGRQ:

WORK HISTORY

Do you
currently work: No

If not, specify
the reason Other

Plasma sample Yes

Total blood sample Yes

END DATE

Date of death: dd/mm/yyyy

Cause of death:

Other cause, specify:

Was an autopsy carried out:

ATTACHMENT E

REGISTRO ESPAÑOL DE PACIENTES CON DEFICIT DE ALFA-1 ANTITRIPSINA	
<input type="checkbox"/> REGISTRO DE PACIENTES <input type="checkbox"/> Registrar nuevo paciente <input type="checkbox"/> Listado de pacientes <input type="checkbox"/> Situación actual del Registro <input type="checkbox"/> Estudios en fase de realización o desarrollo <input type="checkbox"/> Publicaciones <input type="checkbox"/> Preguntas abiertas <input type="checkbox"/> Proleptina <input type="checkbox"/> Trypsone <input type="checkbox"/> Envíos de muestra <input type="checkbox"/> SALIR DEL REGISTRO >>	<div>MODIFICAR DATOS DE PACIENTE</div> <div>Ver seguimientos : Nuevo seguimiento ></div> <p>Por favor, siga las siguientes reglas para la introducción de datos:</p> <p>Utilice el signo PUNTO para indicar decimales: (Ej.: 34.203)</p> <p>Indique las fechas siempre con el formato dd/mm/aaaa: (Ej: 23/02/2001)</p> <p>PACIENTE Nº: 206 INICIALES PACIENTE: RAF</p> <p>Código de país: E Fecha de inclusión: 04/02/2002</p> <p>DEMOGRAFÍA</p> <p>Fecha de nacimiento: 12/04/1947 dd/mm/aaaa Sexo: Female Altura: 149 Unidades de altura: Cm Peso (kg): 57 kilos</p> <p>TABAQUISMO</p> <p>Fumó alguna vez? No Edad de inicio: años Dejó de fumar? Edad en que dejó de fumar años Consumo medio de cigarrillos diarios: Consumo medio de cigarrillos diarios: Pipe - g/semana:</p> <p>MOTIVO DE LA DETERMINACIÓN DE AAT</p> <p>Motivo para determinación de AAT: Family screening Fenotipo: Z Otro fenotipo deficiente:</p> <p>Fecha del diagnóstico del déficit AAT: 18/07/1984 dd/mm/aaaa</p> <p>HISTORIA CLÍNICA</p> <p>Enfermedad pulmonar: Yes Bronquitis crónica: Yes Enfisema: Yes Asma: Yes Bronquiectasias: Yes Otra enfermedad pulmonar? No Especificar: Años: 35 Meses: Edad al inicio de los síntomas respiratorios Síntoma principal: Attacks of dyspnoea</p>

OTROS DIAGNÓSTICOS Yes

Diagnóstico 1: fibromialgia reumática

ICD código diagnóstico 1: Ver Tabla de códigos

ICD versión:

Diagnóstico 2:

ICD código diagnóstico 2: Ver Tabla de códigos

ICD versión:

Diagnóstico 3:

ICD código diagnóstico 3: Ver Tabla de códigos

ICD versión:

Trasplante de pulmón: No

Fecha del trasplante de pulmón: dd/mm/aaaa

Reducción de volumen pulmonar: No

Fecha de reducción de volumen pulmonar: dd/mm/aaaa

Trasplante de hígado: No

Fecha del trasplante de hígado: dd/mm/aaaa

Ha sufrido neumonías? No

En caso afirmativo, ¿Cuántas veces?

Número desconocido

DATOS TC

TC del tórax: Yes

Fecha del TC de tórax: 14/01/1994
dd/mm/aaaa

TRATAMIENTO ACTUAL

Medicación para la enfermedad pulmonar: Yes

Oxigenoterapia domiciliaria: No

TRATAMIENTO SUSTITUTIVO

Alguna vez ha recibido tratamiento sustitutivo? Yes

Fecha de inicio: 13/12/1992
dd/mm/aaaa

Dejó el tratamiento? No

Fecha de interrupción: dd/mm/aaaa

FUNCIONALISMO PULMONAR

Fecha de las primeras pruebas disponibles: 19/06/1988
dd/mm/aaaa

FEV1 pre-broncodilatador (L): 1,3 litros

FEV1 post-broncodilatador (L): 1,4 litros

FVC pre-broncodilatador (L): 2,2 litros

FVC post-broncodilatador (L): 2,3 litros

VC lenta pre-broncodilatador (L): 2,2 litros

VC lenta post-broncodilatador (L): 2,3 litros

Fecha de los pruebas más recientes: 14/12/2001
dd/mm/aaaa

FEV1 pre-broncodilatador (L): 1,7

FEV1 post-broncodilatador: 1,9 litros

FVC pre-broncodilatador (L): 2,3

FVC post-broncodilatador: 2,3 litros

VC lenta pre-broncodilatador (L): 2,3 litros

VC lenta post-broncodilatador: 2,3 litros

KCO (%): %

ENZIMAS HEPÁTICAS

Enzimas hepáticas: Yes

Fecha de determinación: 01/01/1999
dd/mm/aaaa

ALAT/SGOT
Elevada: No

ASAT/SGPT
Elevada: No

GGT Elevada: No

FA Elevada: No

DATOS CUESTIONARIO ST GEORGE

Puntuación total
SGRQ:

HISTORIA LABORAL

Trabajo
actualmente: Yes

Si NO,
especifique
el motivo:

Muestra de
plasma? Yes

Muestra de sangre
total? Yes

FECHA FINAL

Fecha de
fallecimiento : dd/mm/aaaa

Causa de
muerte :

Otra causa, especificar:

Se realizó
autopsia:

Modificar Paciente

Cancelar

Patient N°: 206

PATIENT'S INITIALS: RAF

Country code: E Inclusion date: 04/02/2002

DEMOGRAPHICS

Date of birth:	Sex:
12/04/1947 dd/mm/yyyy	Female
Height	Height units
149	Cm
Weight (kg):	
57	kilos

SMOKING HABITS

Have you ever smoked? No Age started: years old

Have you given up smoking? Age stopped: years old

Average daily consumption of cigarettes:

Average daily consumption of cigars:

Pipe - g/week:

REASON FOR DETERMINING AAT

Reason for determining AAT Family screening

Phenotype: Z

Other deficient phenotype:

Date of diagnosis of AAT deficit: 18/07/1984 dd/mm/yyyy

CLINICAL HISTORY

Lung disease Yes

Chronic bronchitis Yes

Emphysema Yes

Asthma Yes

Bronchiectasis Yes

Other lung disease No Specify

Age respiratory symptoms started	Years old	
Principal symptom	35	Months
Attacks of dyspnoea		

Other diagnosis	Yes		
Diagnosis 1: rheumatic fibromyalgia			
ICD code			
Diagnosis 1	See Code Table	ICD version	
Diagnosis 2			
ICD Code			
Diagnosis 2	See Code Table	ICD version	
Diagnosis 3			
ICD Code			
Diagnosis 3	See Code Table	ICD version	
Lung transplant		Date of lung transplant:	dd/mm/yyyy
Reduction in lung volume		Date of reduction of lung volume:	dd/mm/yyyy
Liver transplant:		Date of liver transplant:	dd/mm/yyyy
Have you suffered from pneumonia?			
If so, how many times?		Unknown number	
TC data			
Thorax TC:	Yes	Date of Thorax TC:	14/01/1994 dd/mm/yyyy
CURRENT TREATMENT			
Medication for lung disease	Yes	Home oxygen therapy:	No
ALTERNATIVE TREATMENT			
Have you received an alternative treatment?	Yes	Start date:	10/07/1995 dd/mm/yyyy
Did you stop treatment?	No	Interruption date	dd/mm/yyyy
PULMONARY FUNCTIONING			
Date of first tests available	19/06/1986	dd/mm/yyyy	
FEV1 pre-bronchodilator 1.3 (L):	litres	FEV1 post-bronchodilator (L)	1.4 litres
FVC pre-bronchodilator 2.2 (L):	litres	FVC post-bronchodilator (L)	2.3 litres
Slow VC pre-bronchodilator 2.2 (L):	litres	Slow VC post-bronchodilator (L)	2.3 litres
Date of most recent tests	14/12/2001	dd/mm/yyyy	
FEV1 pre-bronchodilator 1.7 (L):	litres	FEV1 post-bronchodilator (L)	1.9 litres
FVC pre-bronchodilator 2.3 (L):	litres	FVC post-bronchodilator (L)	2.3 litres
Slow VC pre-bronchodilator 2.3 (L):	litres	Slow VC post-bronchodilator (L)	2.3 litres
KCO (%):	%		
HEPATIC ENZYMES			
Hepatic enzymes: Yes		Date of determination: 01/01/1999	dd/mm/yyyy

High
ALAT/SGOT No

High
ASAT/SGPT No

High GGT No

High FA No

ST GEORGE QUESTIONNAIRE DATA

Total score
SGRQ:

WORK HISTORY

Do you
currently work: Yes

If not, specify
the reason

Plasma sample Yes

Total blood sample Yes

END DATE

Date of death: dd/mm/yyyy

Cause of death:

Other cause, specify:

Was an autopsy carried out:

ATTACHMENT F

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Ongoing research in Europe: Alpha One International Registry (AIR) objectives and development

R. A. Stockley¹, M. Luisetti², M. Miravittles³, E. Piitulainen⁴, P. Fernandez⁵ on behalf of the Alpha One International Registry (AIR) group

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Keywords: Augmentation therapy, chronic obstructive pulmonary disease, emphysema, epidemiology, prevalence, registries

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Accepted: October 22, 2006

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• [ABSTRACT](#)
▼ [METHOD](#)
▼ [RESULTS](#)
▼ [DISCUSSION](#)
▼ [APPENDIX: ALPHA ONE...](#)
▼ [REFERENCES](#)



ABSTRACT

In 1997, the World Health Organization recommended establishing an international registry of α_1 -antitrypsin deficiency. The objective of the present article is to describe the organisation of an international network of registries, the Alpha One International Registry (AIR), and the processes of enrolling and entering data.

By the end of 2005, the registry included individuals from 21 countries (from four continents). The inclusion criterion was either phenotypes PiZZ, PiSZ or other

severely deficient variants. Demographic and clinical information have been collected by a standardised questionnaire, translated for each country. Data are transferred to the AJR database at the Dept of Respiratory Medicine, University Hospital, Malmö, Sweden, either by e-mail or *via* two web-enabled questionnaires in HTML. All data are merged and checked for consistency and missing values.

Collection of data started in 1999 and, by September 2005, data on 2,150 individual patients (1,180 male) had been submitted. Of these, 1,855 (84%) have phenotype PiZ, 181 (8%) PiSZ and 114 (5%) other rare Pi phenotypes. The mean age at inclusion was 49.8 yrs (sd = 13.3) and the majority were Index cases (64.1%).

The Alpha One International Registry is the largest specific α_1 -antitrypsin deficiency registry, fulfilling a major World Health Organization recommendation. The success related to the convergence of national registries into a common database creating a unique registry beyond geographic boundaries and encompassing α_1 -antitrypsin deficiency from various ethnic groups.

Although often regarded as a rare disorder, α_1 -antitrypsin deficiency (α_1 -ATD) is the most common of inherited deficiency states in the Western hemisphere, an apparent contradiction explained by widespread underdiagnosis. The condition was first identified in 1963 and is known to predispose to severe panlobular emphysema, cirrhosis, liver carcinoma and, less commonly, vasculitis and panniculitis 1. The present understanding of its genetic basis and the availability of simple screening and diagnostic tests offer a largely neglected opportunity to identify those with the deficiency who have developed severe pulmonary or hepatic disease. However, they also permit identification of deficient and undetected family members prior to the onset of disease, at a time when preventive measures can be most effective.

The major handicap to understanding and designing interventions is the relative infrequency (one in 1,600 to one in 2,000 in Europe) of the disorder, which has precluded the recruitment and study of sufficient patients for meaningful, adequately powered studies 2. In 1997, the World Health Organization (WHO) published state-of-the-art documentation 3 following a meeting of experts, and

identified questions that remained to be answered. A key recommendation was the establishment of national and international registries to enable data collection, collaborative research and, most specifically, a patient resource for the design and conduct of suitably powered clinical trials. This latter process required the novel design of collection methods for centralisation of data and an unprecedented international collaboration. The Alpha One International Registry (AIR) was initiated to comply with the WHO recommendation to establish an international registry of α_1 -ATD, characterised in as standardised a way as possible by employing a common database. The main objectives of the registry were as follows: 1) to establish an international database of patients and their demographic details; 2) to promote basic and clinical research into α_1 -ATD and to coordinate the activity; 3) to collect, assess and disseminate information concerning all aspects of α_1 -ATD; and 4) to encourage support and awareness of α_1 -ATD. The present article describes the methods and format of this unique database.

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METHOD

Organisation of the registry

AIR was founded in 1997 and included an initial group of European countries (the UK, Germany, Denmark, Sweden, the Netherlands, Italy, Spain and Switzerland), along with New Zealand, South Africa, Canada and a part of the USA. Other countries have since joined, including Denmark, Austria, Belgium, Australia, Poland, Finland, Latvia, Lithuania, Argentina and Brazil. By 2005, the registry included 21 countries from four continents.

The constituent parts of the registry are the general members, the council and the coordinating committee. Each national registry is represented on the council by one national delegate. This national delegate ensures the liaison between the national registry and AIR. The coordinating committee directs and conducts the general activities of AIR, and comprises a chairman, secretary, treasurer and two other members, all elected by the council.

AIR organises at least two annual administrative meetings, as well as a scientific meeting every 2 yrs to provide an update on research progress related to α_1 -ATD 4.

Collection of data

All data in the registry are collected according to national and international rules of confidentiality of personal data and following approval by the corresponding Independent Review Boards. Confidentiality of the data is assured by coding the included patients with an identification number consisting of a six-digit field (four digits for the national registry number and two corresponding to each national telephone code).

The sole inclusion criterion for the registry is the presence of phenotype PIZZ, PiSZ or other severely deficient variants (serum α_1 -antitrypsin (α_1 -AT) concentrations $<11 \mu\text{M}$). From the beginning of the registry until 2005, only individuals aged >18 yrs were included, although from 2005 this age limit has been rescinded.

The questionnaire (available from the present authors by request) consists of standard demographic information (including age and sex), current and previous smoking history to calculate pack-yrs, a pulmonary history with the main symptoms, respiratory medication, the α_1 -AT phenotype, reasons for α_1 -ATD assessment, information on augmentation therapy, lung function (including pre- and post-bronchodilator spirometry, lung volumes and carbon monoxide gas transfer) and liver function tests (γ -glutamyl transferase, alanine transferase and aspartate transferase), comorbidities, whether the patient has undergone lung and/or liver transplantation and specific health-related quality of life measured by the St. George's Respiratory Questionnaire, social status and other diagnoses classified by the International Classification of Diseases code. The patients are followed up annually and information is collected to document

changes in characteristics of the disease, treatment, smoking habits and lung and liver function. The original English-language version of the questionnaire has been translated and adapted into the appropriate language for each country.

Transmission and validation of data

The database and data manager are located at the Dept of Respiratory Medicine, University Hospital, Malmö, Sweden. Data from the national registries are transferred periodically to the AIR database. Initially, the questionnaire was incorporated in a Microsoft Access sheet and each national delegate collected their own data and submitted it to the data manager by encrypted e-mail or by delivery of electronic media. All data were downloaded into a unique database and were checked by the national coordinator for consistency. The database manager then reviewed the data submitted and checked with the national coordinator if data was missing or calculated lung function appeared at variance. At the present time, data from Germany, Italy, Sweden and Canada are still periodically transferred to the central database using this process. Each national coordinator is able to review their own entries. An update of the data from all countries is presented at each AIR meeting and searched to answer specific queries raised by the council. The database cannot be accessed by a third party.

As early as 1999 it was recognised that some countries would experience great difficulty in centralising the collection of data in a single centre. Spain developed a web-enabled questionnaire in HTML, which was the interface for a database in Oracle, hosted at the web page of the National Society of Chest Physicians (SEPAR). By using a username and a password every physician in the country caring for an α 1-ATD individual was able to access the web page and complete the questionnaire online. The national delegate has a special user access and can check the quality of data whilst preserving the confidentiality. The Oracle database is adapted to the format text delimited as requested by the central data manager and submitted (encrypted) twice a year from 2001, to the central database in Malmö. The same web-enabled questionnaire in Spanish has been used from 2003 by the Argentinean registry, and the Portuguese translation has been used by the Brazilian registry from 2005.

Another web-enabled database was developed in the Netherlands in 2000, and is available in the UK, Switzerland, the USA, New Zealand, Australia, South Africa, Austria, Belgium and Poland. Data collected in these countries are submitted to the Netherlands and then periodically to the central database in Sweden.

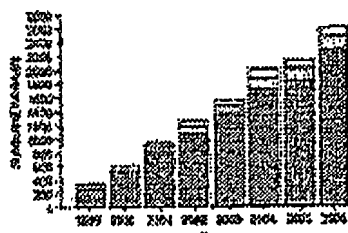
All data downloaded to the central database are merged in a single database and checked for consistency and missing values by the data manager. Queries are sent to the national representatives for completion and resolution.

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▶ **RESULTS**

The number of patients for whom data has been submitted to the central database is shown in figure 1*. Collection of data began in 1999 and by September 2005, data from 2,150 α_1 -AT-deficient individuals (1,180 male, 968 female) had been submitted (in two subjects the sex was not reported). Of these subjects, 1,855 (84%) have phenotype PiZ, 181 (8%) phenotype PiSZ, and 114 (5%) have other rare Pi phenotypes with severe α_1 -ATD. A total of 45 (2%) subjects have been excluded at present, as the Pi phenotype has yet to be reported, and 16 subjects have been excluded because of an inappropriate Pi phenotype (PiMZ, PiSS, *etc.*). Table 1* shows the number of subjects by country and the year when each country included its first patient (updated March 2006). The mean age of the subjects was 49.8 yrs (range 0–100 yrs; sd 13.3 yrs) at inclusion, although the age has yet to be submitted for 17 of the patients. The initial reasons for the α_1 -AT analyses are shown in table 2*. Table 3* compares the characteristics of patients in the AJR with those of patients in two large North American databases: the National Heart, Lung, and Blood Institute (NHLBI)

Registry and the Alpha One Foundation Research Network Registry (AOF-RNR).



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Fig. 1— Cumulative increase of the Alpha One International Registry. By March 2006, a total of 2,527 α_1 -antitrypsin (A1) deficient individuals (2,285 PIZZ, 218 PiSZ, and 124 other rare α_1 -AT deficient phenotypes) were included in the register. ■ Pi other, ■ PiSZ, ■ box-HiPi, PIZZ

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Table 1— The number of patients included in the Alpha One International Registry by country, last updated March 2006

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Table 2— The initial reasons for α_1 -antitrypsin analysis

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Table 3— Characteristics of α_1 -antitrypsin deficiency (α_1 -ATD) subjects included in the Alpha One International Registry (AIR), the National Heart, Lung, and Blood Institute (NHLBI) registry, and the Alpha One Foundation Research Network Registry (AOF-RNR)

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DISCUSSION

In the present paper, the successful implementation of a major recommendation made by the 1996 WHO workshop on α_1 -ATD is described 3. Registries of individuals fulfilling careful diagnostic and assessment criteria, and enrolled on a national basis under the supervision of an expert database manager make available populations in whom understanding of this rare disease (*i.e.* disorders, such as α_1 -AT, characterised by a prevalence of <5 out of 10,000 subjects) can be furthered. The success of AIR has been the convergence of national registries into a common database combining agreed information, thus creating a unique registry beyond geographical boundaries and encompassing α_1 -ATD from varying ethnic groups. This is of particular relevance, since it has recently been shown that α_1 -ATD is not confined to Northern European populations and their descendants alone but is a disorder with a worldwide distribution 5, 6. The development of a shared questionnaire, the adoption of a minimum requirement to ensure a quality control, and the electronic transfer of data, either by encrypted e-mail shipment of Access sheets or by a secure web-enabled database, greatly contributed to the success of AIR data validation, dissemination and rapid growth.

With 2,627 subjects enrolled (last updated March 2006; fig. 1+), AIR is the largest and most comprehensive registry for α_1 -ATD (PiZ phenotype). Two other large registries for α_1 -ATD exist; both are located in North America. The NHLBI Registry for Individuals with severe α_1 -ATD completed recruitment in 1996 and included 1,129 subjects, with the main goal of characterising the natural history of α_1 -ATD, and with the rate of lung function decline and survival as major aims 7. The AOF-RNR is a separate registry; participating subjects have expressed a willingness to be approached for participation in studies, including randomised clinical trials 8. A board of physicians/investigators and patient advocates ensures data quality control; by 2001, the AOF-RNR included 1,204 individuals, although the phenotype is self-reported and hence contains unconfirmed PiZ patients. Besides differences concerning structure and enrolment mechanisms,

a major, intuitive difference between AIR and the two Northern American α_1 -ATD registries is geography. AIR enrollees are mostly Europeans (1,745; 81% of the total included). Taking into account that 204 α_1 -ATD subjects in the AIR are from the USA and Canada (and therefore they might be also present in both NHLBI and AOF registries), AIR includes a cohort of $\geq 90\%$ α_1 -ATD subjects that differs from that of the two Northern American registries. However, comparing some characteristics of the α_1 -ATD series in AIR (current results) with the published ones in the NHLBI series 7 and in the AOF registry 8, there is a general concordance of basic characteristic data (table 3+). The disorder is usually diagnosed within the fifth decade of life and there is a slight preponderance of male subjects. The rate of ascertainment for family screening (more recently referred to as predispositional testing) 9 is similar between AIR and the NHLBI registry (19.2 and 19.8%, respectively). The main difference between the two registries is the distribution of α_1 -ATD phenotypes. AIR included a lower percentage of PI*Z subjects than the NHLBI registry (86.2 *versus* 97.3%, respectively). Furthermore, the PI*SZ and rare genotypes are eight- and three-fold higher in AIR, respectively. This might reflect the different epidemiology of S and rare α_1 -ATD variants in the European countries 2, 5, 6, 10, 11 or different inclusion criteria. Comparison with the AOF-RNR is, however, uncertain with reference to phenotype, since the AOF-RNR registry includes mainly self-reported deficiency patients and includes intermediate (PI*MZ) and undetermined phenotypes, whereas those in AIR are confirmed. Finally, the smoking habit is similar among all three registries, although the lower rate of active smoking in the AOF-RNR may reflect the higher rate of awareness about smoking cessation in the self-reported patients. Detailed analysis of these and other characteristics of the α_1 -ATD subjects in AIR will be the subject of future publications.

There are some features of the AIR development that exceed those of a simple registry for a rare disease. First, AIR has facilitated collaboration between clinicians from 21 different countries in four continents, 18 of which have already entered patients to the registry (table 1+). Existing national registries for α_1 -ATD, such as those in Sweden, the UK, Spain 12 and the Netherlands, joined other registries, such as that in Italy, that were established to join the AIR on its

formation. More recently, registries have joined as they have been formed in response to the AIR. Thus, AIR has played a central role in raising awareness of α_1 -ATD in countries with medium-to-low prevalence of the disorder. Secondly, AIR and its scientific initiatives, such as the international conferences 4, have not only gathered clinicians concerned with α_1 -ATD but have also encouraged a number of scientists, including geneticists, epidemiologists, biochemists and pathologists, as well as representatives of patient support groups, public health and pharmaceutical companies, to collaborate with a common goal. It is clear that such synergy is critical for significant advances in and a better understanding of α_1 -ATD, its pathogenesis, its current management and the development of novel therapeutic strategies, with a patient database needed to successfully deliver clinical trials (in this uncommon condition). In this respect, two such trials are currently underway: EXACTLIE (Exacerbations and Computer Tomography in Laurell's syndrome as Investigative Endpoints), which is a 2-yr, placebo-controlled intravenous augmentation study and REPAIR (Retinoids for Emphysema Patients and Alpha-1-antitrypsin International Registry), a 12-month trial of a retinoic acid receptor- γ agonist. In addition, the consortium has been successful in obtaining two European Union grants (AIR genetics and SPREAD (grant number RNDV07773). Finally, data gathered *via* AIR and, in particular, in the UK and Canadian registries has led to a new study confirming a beneficial effect of augmentation therapy for emphysema arising from α_1 -ATD and to a meta-analysis of this and published studies of α_1 -ATD 13, 14.

In conclusion, a major international collaboration is described herein that has provided a common database to advance in understanding and treatment of α_1 -antitrypsin deficiency.

APPENDIX ALPHA ONE INTERNATIONAL REGISTRY (AIR) GROUP

Structure of AIR

AIR Chairman: J. Stolk (the Netherlands).

Past chairmen: N. Konietzko (Germany) and R.A. Stockley (UK).

Council: M. Luisetti (Italy), M. Miravittles (Spain), E.

Piitulainen (Sweden), P. Fernandez (UK), K.R. Chapman (Canada), A. Dirksen (Denmark), J. Houtsebaert (Belgium), J. Jardim (Brazil), G. Menga (Argentina), C. Vogelmeier (Germany), J. Zielinski (Poland), G. Ainslie (South Africa), E.W. Russi (Switzerland), E. Campbell (USA), M. Epton (New Zealand), K. Schmid (Austria), A. Krams (Latvia), M. Zolubas (Lithuania), S. Saarelainen (Finland) and J. Burdon (Australia).

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REFERENCES

1. Stockley RA. α_1 -Antitrypsin: more than just deficiency. *Thorax* 2004;59:363–364. [[Free Full Text](#)]
2. Blanco I, de Serres FJ, Fernández-Bustillo E, Lara B, Miravittles M. Estimates of the prevalence of α_1 -antitrypsin deficiency PI*S and PI*Z alleles and the numbers at risk in Europe countries. *Eur Respir J* 2006;27:77–84. [[Abstract/Free Full Text](#)]
3. World Health Organization. Memoranda. α_1 -Antitrypsin deficiency: memorandum from a WHO meeting. *Bull WHO* 1997;75:397–415. [[ISI](#)][[Medline](#)] [[Order article via Infotrieve](#)]
4. Luisetti M, Miravittles M, Stockley RA. α_1 -Antitrypsin deficiency: a report from the 2nd meeting of the Alpha One International Registry, Rapallo (Genoa, Italy), 2001. *Eur Respir J* 2002;20:1050–1056. [[Abstract/Free Full Text](#)]

5. de Serres FJ. Worldwide racial and ethnic distribution of α_1 -antitrypsin deficiency. Summary of an analysis of published genetic epidemiology surveys. *Chest* 2002;122:1818-1829. [[Abstract/Free Full Text](#)]
6. Luisetti M, Seersholm N. α_1 -antitrypsin deficiency. 1: Epidemiology of α_1 -antitrypsin deficiency. *Thorax* 2004;59:164-169. [[Abstract/Free Full Text](#)]
7. McElvaney NG, Stoller JK, Buist SA, *et al*. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of α_1 -antitrypsin deficiency. *Chest* 1997;111:394-403. [[Abstract/Free Full Text](#)]
8. Stoller JK, Brantly M, Fleming LB, Bean JA, Walsh J. Formation and current results of a patient-organized registry for α_1 -antitrypsin deficiency. *Chest* 2000;118:843-848. [[Abstract/Free Full Text](#)]
9. American Thoracic Society/European Respiratory Society. American Thoracic Society/European Respiratory Society Statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003;168:818-900. [[Free Full Text](#)]
10. Ferrarotti I, Baccheschi J, Zorzetto M, *et al*. Prevalence and phenotype of subjects carrying rare variants in the Italian registry for alpha₁-antitrypsin deficiency. *J Med Genet* 2005;42:282-287. [[Free Full Text](#)]
11. De Serres FJ, Blanco I, Fernandez-Bustillo E. Genetic epidemiology of alpha-1 antitrypsin deficiency in southern Europe: France, Italy, Portugal and Spain. *Clin Genet* 2003;63:490-509. [[CrossRef](#)][[ISI](#)][[Medline](#)] [[Order article via Infotrieve](#)]
12. Miravittles M, Vidal R, Barros-Tizón JC, *et al*. Usefulness of a national registry of alpha-1-antitrypsin deficiency. The Spanish experience. *Respir Med* 1998;92:1181-1187. [[CrossRef](#)][[ISI](#)][[Medline](#)] [[Order article via Infotrieve](#)]
13. Chapman KR, Bradi AC, Paterson D, Navickis RJ, Wilkes MM. Slower lung function decline during augmentation therapy in patients with alpha1-antitrypsin deficiency (A1ATD): results from the Canadian AIR registry. *Proc Am Thorac Soc* 2005;2:A808
14. Chapman KR, Stockley RA, Wilkes MM, Navickis RJ. The value of augmentation therapy for α_1 -antitrypsin deficiency: a meta-analysis. *Respir Care* 2005;50:1550